



**AFRL-SA-WP-TP-2013-0002**

# **Effects of Aeromedical Evacuation on the Host Response in Seriously Injured Casualties**



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**September 2013**

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Case Number: 88ABW-2013-5294,  
13 Dec 2013**

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<b>REPORT DOCUMENTATION PAGE</b>				Form Approved OMB No. 0704-0188	
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<b>1. REPORT DATE (DD-MM-YYYY)</b> 4 Sep 2013		<b>2. REPORT TYPE</b> Technical Paper		<b>3. DATES COVERED (From – To)</b> August 2010 – August 2013	
<b>4. TITLE AND SUBTITLE</b>  Effects of Aeromedical Evacuation on the Host Response in Seriously Injured Casualties				<b>5a. CONTRACT NUMBER</b> FA8650-10-2-6B01	
				<b>5b. GRANT NUMBER</b>	
				<b>5c. PROGRAM ELEMENT NUMBER</b>	
<b>6. AUTHOR(S)</b> Timothy Pritts, MD				<b>5d. PROJECT NUMBER</b> F1J5AF0175B001	
				<b>5e. TASK NUMBER</b>	
				<b>5f. WORK UNIT NUMBER</b>	
<b>7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)</b> University of Cincinnati Sponsored Research Services 51 Goodman Drive, Suite 530 Cincinnati, OH 45221-0222				<b>8. PERFORMING ORGANIZATION REPORT NUMBER</b>	
<b>9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)</b> USAF School of Aerospace Medicine Air Force Expeditionary Medical Skills Institute/C-STARS Cincinnati 2510 Fifth St. Wright-Patterson AFB, OH 45433-7913				<b>10. SPONSORING/MONITOR'S ACRONYM(S)</b>	
				<b>11. SPONSOR/MONITOR'S REPORT NUMBER(S)</b> AFRL-SA-WP-TP-2013-0002	
<b>12. DISTRIBUTION / AVAILABILITY STATEMENT</b>  Distribution A: Approved for public release; distribution is unlimited. Case Number: 88ABW-2013-5294, 13 Dec 2013					
<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Previous studies have demonstrated that aeromedical evacuation (AE) can increase local and systemic inflammation after severe injury. How different components of AE, such as hypoxia, pressure, noise, vibration, and G-forces, affect the inflammatory response to severe injury is unknown. Previous studies suggest that AE occurring rapidly after injury may have greater effects on the inflammatory response after severe injuries, such as hemorrhage/resuscitation, burn injury, and moderate traumatic brain injury, and may provide insight into the “ideal time-to-fly.” Therapeutic targeting of inflammatory mediators to reduce AE effects on inflammation has not been studied. Such studies may identify treatments that can protect against AE-induced inflammation and allow rapid AE. The effect of AE on susceptibility to infection is unknown. Our previous Air Force-funded work has shown that AE induces the expression of mediators that may suppress immune function and therefore increase the risk of post-transport infection. The manner in which AE may induce immunosuppression is unclear. Previous work has demonstrated that resuscitation with aged blood products exacerbates systemic inflammation. This work has identified potential inflammatory mediators that could be targeted for therapeutic intervention. It is unknown whether blockade of these mediators would extend the age effectiveness of blood products and therefore ease the logistical problems of blood transport to theater.					
<b>15. SUBJECT TERMS</b> Aeromedical evacuation, inflammatory mediators, systemic inflammation					
<b>16. SECURITY CLASSIFICATION OF:</b>			<b>17. LIMITATION OF ABSTRACT</b>  SAR	<b>18. NUMBER OF PAGES</b>  5	<b>19a. NAME OF RESPONSIBLE PERSON</b> Dr. Timothy Pritts
<b>a. REPORT</b> U	<b>b. ABSTRACT</b> U	<b>c. THIS PAGE</b> U			<b>19b. TELEPHONE NUMBER (include area code)</b>

## **1.0 SUMMARY**

This project addressed gaps in knowledge regarding the effects of aeromedical evacuation on host response to injury, including local and systemic inflammation, infection, and secondary injury. Stakeholders were the Air Mobility Command, Air Combat Command, and Air Force Special Operations Command. Our overall aim was to understand how aeromedical evacuation affects local and systemic inflammation, infection, and the susceptibility of casualties to secondary injury and determine “ideal time-to-fly” for injured casualties.

## **2.0 INTRODUCTION**

Previous studies have demonstrated that aeromedical evacuation (AE) can increase local and systemic inflammation after severe injury. How different components of AE, such as hypoxia, pressure, noise, vibration, and G-forces, affect the inflammatory response to severe injury is unknown. Previous studies suggest that AE occurring rapidly after injury may have greater effects on the inflammatory response after severe injuries, such as hemorrhage/resuscitation, burn injury, and moderate traumatic brain injury (TBI), and may provide insight into the “ideal time-to-fly.”

Therapeutic targeting of inflammatory mediators to reduce AE effects on inflammation has not been studied. Such studies may identify treatments that can protect against AE-induced inflammation and allow rapid AE. The effect of AE on susceptibility to infection is unknown. Our previous Air Force-funded work has shown that AE induces the expression of mediators that may suppress immune function and therefore increase the risk of post-transport infection. The manner in which AE may induce immunosuppression is unclear.

## **3.0 METHODS**

Four specific aims were proposed to gain a further understanding on how AE affects local and systemic inflammation, infection, and susceptibility of casualties to secondary injury and to determine the “ideal time-to-fly” for injured casualties. These aims are as follows:

1. Conduct studies that provide the scientific basis for the “ideal time-to-fly” for severely injured casualties
2. Conduct studies that develop potential therapeutic strategies to limit AE-induced inflammation
3. Conduct studies that determine how AE causes increased susceptibility to infection and develop potential treatments to reduce immunocompromise
4. Conduct studies that determine how aged blood products alter the host response during resuscitation to develop potential adjuncts that can extend the effectiveness of aged blood products

## **4.0 RESULTS/DISCUSSION**

In this paper, experiments conducted along with results will be outlined by specific aim.

#### **4.1 Specific Aim 1: Conduct Studies that Provide the Scientific Basis for the “Ideal Time-to-Fly” for Severely Injured Casualties**

We conducted experiments investigating the impact of simulated AE occurring after different periods of time on local and systemic inflammation after severe injury as well as experiments that investigated the contributions of different components of AE on the augmented inflammatory response observed after severe injury. Our results confirmed our previous findings that simulated early transport after TBI in mice resulted in increased secondary brain injury and worsened neuroinflammation. Additional experiments suggested that hypoxia alone could account for the secondary injury seen from simulated transport. In addition, we found that the period of hypoxia that could lead to secondary brain injury may be as brief as 30 minutes. Subsequent experiments indicate that inflammation can be decreased with ethanol. Together, data from experiments performed in Aim 1 suggest that traumatic brain injury is associated with a neuroinflammatory state and that the injured brain is particularly susceptible to secondary injury from early exposure to hypobaric hypoxia, indicating that the “ideal time-to-fly” should be after the initial period of neuroinflammation has resolved.

#### **4.2 Specific Aim 2: Conduct Studies that Develop Potential Therapeutic Strategies to Limit AE-Induced Inflammation**

We conducted experiments to investigate the effects of blockade of specific inflammatory mediators on AE-induced inflammation after severe injury as well as whether blockade of specific mediators of inflammation can facilitate more rapid AE after severe injury. In initial experiments, we investigated the use of a small dose of ethanol orally prior to and after TBI and found that this decreased neuroinflammation non-specifically. In subsequent experiments that were based on data generated in Aim 1 as well as previous experimental data, we tested blockade of inflammatory mediators on TBI-induced neuroinflammation and identified IL-6 and MIP-1 $\alpha$  as potential candidates for intervention. Subsequent experiments indicated that IL-6 is a key regulator of neuroinflammation and deficits of motor coordination after mild TBI. Blockade of IL-6 resulted in decreased neuroinflammation and mitigation of TBI-induced motor deficits. Subsequently, we demonstrated that IL-6 blockade reduces hypoxia-induced secondary neuroinflammation and motor coordination deficits in the setting of TBI. Together, these data suggest that IL-6 is a potential therapeutic target to limit AE-induced inflammation as well as allow earlier AE without inducing secondary neurological injury. *We feel that these data are particularly compelling and merit additional future study to advance this as a potential treatment strategy after TBI.*

#### **4.3 Specific Aim 3: Conduct Studies that Determine How AE Causes Increased Susceptibility to Infection and Develop Potential Treatments to Reduce Immunocompromise**

We investigated potential mechanisms by which AE induces post-transport susceptibility to infection post injury. These studies focused on the relationship between TBI and pneumonia, as experiments in our hemorrhagic shock model indicated that there is no altered host inflammatory response after hemorrhage and simulated AE. In those experiments, we found that following hemorrhagic shock and resuscitation, flight does not exacerbate systemic

inflammation in our murine model. This was examined at multiple time intervals after hemorrhagic shock. In the TBI model, we found that TBI was associated with decreased pneumonia rates. This was a surprising finding and led to further in-depth investigation. We confirmed this in our murine model. A series of retrospective inquiries to the National Trauma Data Bank confirmed that TBI in humans is associated with lower than anticipated pneumonia rates. Additional work suggests that this may be related to alterations in peripheral substance P.

#### **4.4 Specific Aim 4: Conduct Studies that Determine How Aged Blood Products Alter the Host Response During Resuscitation to Develop Potential Adjuncts that Can Extend the Effectiveness of Aged Blood Products**

We conducted experiments that investigated the manner in which aged blood products alter the inflammatory response and organ injury after severe injury. Our initial experiments evaluated different ratios of plasma to packed red blood cell (pRBC) units during acute resuscitation. Our data suggest that a 1:1 ratio of plasma to pRBC units is the least inflammatory and most physiologic. Our data led us to focus on macrophage-derived chemokine (MDC/CCL22) as a potential mediator of lung injury after hemorrhage and resuscitation. Our experiments suggested that MDC is a novel mediator of lung injury after resuscitation and that blockade of MDC leads to decreased inflammation under these conditions. Additional experiments suggest that MDC acts to encourage neutrophil infiltration into the lung. In additional experiments, we investigated the role of red blood cell microparticles in lung injury after hemorrhage and resuscitation with aged units of packed red blood cells. We found that the microparticles present in these units lead to increased lung injury and increased neutrophil priming after hemorrhage and resuscitation. In other experiments, we examined the use of washing aged blood products on the red blood cell storage lesion. Our data suggest that at least a portion of increased inflammation associated with resuscitation with stored pRBC units can be decreased by washing prior to transfusion. Subsequent experiments suggest that Hextend or Hespan may be useful adjuncts for initial early resuscitation, but this data set is less consistent. *We feel that data generated under this specific aim are of particular importance and that additional work to investigate the role of inflammatory mediators, including microparticles, is merited.*

## **5.0 CONCLUSION**

Results of these experiments have increased our understanding of the effect of injury and simulated aeromedical evacuation on the host response to serious injury. In some cases, results were compelling and warrant further investigation to gain a deeper understanding of these effects on casualties.